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ORIGINAL RESEARCH

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The efficacy of TP chemotherapy combined with karelizumab on the postoperative clinical status of patients with advanced ovarian cancer

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Abstract

To investigate the efficacy of TP (Toripalimab Plus) chemotherapy combined with karelizumab in the treatment of advanced ovarian cancer after surgery. We recruited 96 patients with advanced ovarian cancer who were admitted to our hospital between December 2019 and December 2022 with advanced ovarian cancer and treated by tumor cell reduction surgery. The patients were randomly divided into groups using a digital table, 48 each. The control group was treated with chemotherapy, while the observation group was treated with chemotherapy combined with karelizumab. We compared the two groups with regards to adverse reactions and the levels of VEGF (Vascular Endothelial Growth Factor), MMP-9 (matrixmetalloproteinase 9), CEA (A Carcinoma Embryonic Antigen), AFP (alpha-fetoprotein), CA125 (carbohydrate antigen 125), CA19-9 (carbohydrate antigen 19-9) and T lymphocytes. There was no significant difference between the two groups with regards to adverse reactions ($p > 0.05$); the levels of VEGF and MMP-9 in the observation group were lower. There was a significant difference between the data before and after treatment within the same group (all $p < 0.05$); the levels of CEA, AFP, CA125 and CA19-9 in the observation group were lower than those in the control group, with significant differences before and after treatment within the same group ($p < 0.05$); the levels of CD3+ (cluster of differentiation 3+) and CD4+ in the observation group were higher, while the levels of CD8+ were lower than those in the control group. There were significant differences before and after treatment in the same group ($p < 0.05$). The combination of karelizumab and TP chemotherapy had a significant and positive impact on postoperative patients with advanced ovarian cancer by effectively regulating immune function and the levels of tumor markers. This protocol is safe and can be selected by considering the specific situation of individual patients.

Keywords

Advanced ovarian cancer; Karelizumab; TP chemotherapy; Adverse reactions; T lymphocyte subgroup

1. Introduction

Advanced ovarian cancer is a common clinical disease that threatens the health and life of patients. Timely treatment is required to control the development of this condition [1]. Currently, the combination of cytoreductive surgery and chemotherapy is the main treatment for this disease, and the effects of this treatment are relatively good. This treatment regimen can control tumors, slow down the growth of tumors and prolong a patient's life [2]. TP chemotherapy is the commonly used strategy and has an obvious effect on cancer. It mainly includes paclitaxel and cis-platinum. Paclitaxel can damage the microvessels of tumor cells and inhibit their growth. Cis-platinum will bind to the DNA of tumor cells to generate protein DNA cross-linking and reduce its replication. However, the therapeutic effect of TP chemotherapy alone is limited. Meanwhile, when patients are received more chemotherapies, they will have more drug resistance, and the chemotherapy will also cause damage to the body's immune system and healthy cells. However, the maximum plasma concentration does not persist for long and some patients develop high levels of drug resistance. These factors may impact the overall curative effect [3]. Previous studies have shown that, most ovarian cancer cells can escape from the immune system and tumor growth is promoted *via* different mechanisms, including the immune checkpoint PD-1/PD-L1 (programmed cell death protein 1/programmed death ligand 1). While the high expression of PD-L1 in ovarian cancer cells often indicates poor prognosis. The expression of PD-L1 in ovarian cancer ascites and blood mononuclear

cells is associated with poor clinical prognosis. Meanwhile, experimental data also show that anti-PD-1/PD-L1 pathway antibodies are beneficial to patients with advanced ovarian cancer. By regulating human immune response, immune-targeted therapy has achieved effective results in the treatment of highly microsatellite instability ovarian cancer, mismatch repair tumors and other refractory malignant tumors. With the continuous progress of medical research, karelizumab has been found to have certain advantages for the treatment of ovarian cancer. This drug is a PD-1 inhibitor and blocks binding between PD-1 and its receptors; it also activates T lymphocytes and the immune response to avoid the excessive growth of tumors [4]. At present, there are few studies about TP chemotherapy combined with karelizumab in the treatment of advanced ovarian cancer. Thus, in order to study the efficacy of TP chemotherapy combined with karelizumab for the treatment of advanced ovarian cancer after surgery, we selected 96 patients with advanced ovarian cancer who were treated in our hospital from December 2019 to December 2022 to conduct this study.

2. Material and Methods

2.1 Basic information

We recruited a total of 96 patients with advanced ovarian cancer who were treated in the Affiliated Jiangyin Hospital of Nantong University between December 2019 and December 2022. In accordance with the random number table, the patients were divided into two groups, each containing 48 patients. Table 1 shows basic information relating to the patients ($p > 0.05$).

The inclusion criteria were as follows: (1) patients were diagnosed with advanced ovarian cancer by medical examination and (2) the patients and their families were informed of this research. Patients were excluded if they had other tumors, hematological diseases, or chemotherapy contraindications.

2.2 Methods

All patients were carefully examined and underwent cytoreductive surgery for ovarian cancer. Patients in the control group were given TP chemotherapy for three weeks after the surgery. These patients were given 135 mg/m^2 of paclitaxel (H20193309, Qilu Pharmaceutical Co., Ltd, Hainan, China) on the first day for 3 hours, and then 70 mg/m^2 cisplatin (H37021358, Qilu Pharmaceutical Co., Ltd, Hainan, China). The chemotherapeutic cycle was 21 days and the patients received three cycles. Patients in the observation group were given TP chemotherapy and 200 mg of karelizumab (S20190027, Suzhou Suncadiabio Co., Ltd, Suzhou, China) half an hour before the first day of each chemotherapy period.

2.3 Indicators

2.3.1 Adverse reactions

Patients' adverse reactions were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE v3.0) published by American National Cancer Institute (NCI).

2.3.2 Comparison of vascular endothelial growth factor (VEGF) and matrix metalloproteinase 9 (MMP-9)

The levels of VEGF and MMP-9 prior to treatment were compared with those after treatment. For detection, 4 mL of fasting venous blood was collected from the elbow and collected transferred to test tubes for centrifugation at 4000 RPM (Revolutions Per Minute) for 10 minutes. Serum samples were then collected for testing. If these samples were not checked in time, they would be stored in a refrigerator at −20 °C. Indices were then acquired by enzyme-linked immunosorbent assays.

2.3.3 Tumor markers

Serum samples were collected for detection and a range of tumor markers were determined by chemiluminescence, including CEA, AFP, CA125 and CA19-9.

2.3.4 T lymphocytes

The levels of T lymphocyte subgroups (CD3+, CD4+, CD8+) were determined by automatic flow cytometry.

2.4 Statistics

SPSS 21.0 software (Statistical Package for Social Sciences 21.0, IBM, Armonk, NY, USA) was used to analyze the data. Numerical/frequency (n) data and proportional (%) data were analyzed by the Chi-squared test. Measurement data (mean and standard deviation) were analyzed by the t test. Differences were considered statistically significant if $p < 0.05$.

2.5 Sample size

PASS 15.0 (Power Analysis and Sample Size 15.0, NCSS, Enumclaw, WA, USA) was used to calculate the sample size. The test level α value was set as 0.05, and the test power 1-β value was set as 0.95. According to previous studies, the effective rate of intervention group was 84%, while that of control group was 44%. Thus, the sample size was calculated as 40 cases in each group, a total of 80 cases. Considering sample dropout rate, the size was increased by 20%. Thus, a total of 96 patients were collected.

3. Results

3.1 Adverse reactions

There was no significant difference between two groups in terms of adverse reactions ($p > 0.05$; Table 2).

3.2 Indices

After treatment, the levels of VEGF and MMP-9 in the observation group were significantly lower than those in the control group ($p < 0.05$; Table 3).

3.3 Tumor markers

After treatment, the levels of CEA, AFP, CA125 and CA19-9 in the observation group were significantly lower than those in the control group ($p < 0.05$; Table 4).

TABLE 1. A comparison of basic information between the two groups of patients.

Indicators	Project	Observation group (n = 48)	Control group (n = 48)	χ^2/t	*p* value
Stages					
	Stage III	25	27	0.168	0.682
	Stage IV	23	21		
Self-care					
	Yes	22	23	0.042	0.838
	No	26	25		
Education Background					
	Beyond high school	21	20	0.043	0.837
	Below high school	27	28		
Diseases Types					
	Mucinous carcinoma	18	19		
	Serous carcinoma	22	20	0.181	0.913
	Endometrioid carcinoma	8	9		
Age		52.35 ± 3.64	52.38 ± 3.61	0.041	0.968
Tumor diameter (cm)		3.22 ± 0.75	3.19 ± 0.73	0.199	0.843
BMI (kg/m^2)		23.58 ± 1.15	23.67 ± 1.20	0.375	0.708
KPS		38.54 ± 5.26	38.59 ± 5.24	0.047	0.838

BMI: Body Mass Index; KPS: Karnofsky score.

TABLE 2. Adverse reactions.

Group	Number	Anemia	Nausea and vomiting	Losing hair	Liver injury	Leukopenia	Thyroid dysfunction
Observation group	48	19 (39.58)	30 (62.50)	12 (25.00)	15 (31.25)	23 (47.92)	10 (20.83)
Control group	48	22 (45.83)	28 (58.33)	11 (22.92)	17 (35.42)	22 (45.83)	12 (25.00)
χ^2		0.383	0.174	0.057	0.188	0.042	0.236
p		0.536	0.676	0.811	0.665	0.838	0.627

TABLE 3. Analysis of key indicators.

Indicators	Time	Observation group (n = 48)	Control group (n = 48)	*t*	*p*
Vascular endothelial growth factor (VEGF, pg/mL)					
	Before treatment	57.68 ± 6.92	57.92 ± 6.94	0.170	0.866
	After treatment	25.68 ± 5.03	30.24 ± 5.68	4.164	<0.001
	t	25.915	21.384		
	p	<0.001	<0.001		
Matrix metalloproteinase 9 (MMP-9, ng/mL)					
	Before treatment	815.36 ± 85.57	814.95 ± 85.51	0.023	0.981
	After treatment	435.26 ± 52.28	495.36 ± 59.85	5.240	0.000
	t	26.261	21.214		
	p	<0.001	<0.001		

TABLE 4. Analysis of tumor markers.

Indicators	Time	Observation group (n = 48)	Control group (n = 48)	*t*	*p*
Carcino-embryonic antigen (CEA, ng/mL)					
	Before treatment	25.96 ± 4.35	25.92 ± 4.31	0.045	0.964
	After treatment	14.02 ± 2.52	16.85 ± 2.85	5.154	<0.001
	t	16.455	12.161		
	p	<0.001	<0.001		
Alpha fetoprotein (AFP, ug/L)					
	Before treatment	47.25 ± 5.54	47.22 ± 5.51	0.027	0.979
	After treatment	28.64 ± 4.58	32.25 ± 4.85	3.749	<0.001
	t	17.937	14.129		
	p	<0.001	<0.001		
Carbohydrate antigen 125 (CA125, U/mL)					
	Before treatment	152.36 ± 15.57	151.85 ± 15.24	0.162	0.872
	After treatment	49.65 ± 8.69	59.96 ± 9.02	5.703	<0.001
	t	39.908	35.949		
	p	<0.001	<0.001		
Carbohydrate antigen 19-9 (CA19-9, U/mL)					
	Before treatment	61.25 ± 7.14	61.22 ± 7.08	0.021	0.984
	After treatment	20.25 ± 4.85	26.68 ± 5.68	5.964	<0.001
	t	32.909	26.364		
	p	<0.001	<0.001		

3.4 Analysis of T lymphocyte subgroups

After treatment, the levels of CD3+ and CD4+ in the observation group were significantly higher than those in the control group, while the level of CD8+ was significantly lower than that in the control group ($p < 0.05$; Table 5).

4. Discussion

Ovarian cancer is a common malignant tumor in the clinic, accounting for approximately 23% of all tumors of the genital tract. Over recent years, research has shown that the number of patients developing ovarian cancer has increased, thus threatening patient health and life [5–7]. Ovarian cancer is also the main cause of death in women. However, mechanisms underlying this disease remain unclear, although previous research has suggested a range of factors, including heredity, physiological states, gynecological diseases and other factors. The early symptoms of ovarian cancer are not obvious but become worse as the disease becomes more severe. Consequently, many patients are diagnosed in the advanced stages of disease. The local infiltration of tumor cells is obvious, and tumor cells can easily to metastasize to other areas, such as the pelvis and abdominal cavity. Seroperitoneum can also occur. Thus, ovarian cancer is difficult to treat and is associated with a very poor prognosis [8–10].

At present, cytoreductive surgery is commonly used for the treatment of ovarian cancer. Following surgery, chemotherapy is often necessary to consolidate the treatment, so as to improve the overall effect and improve the prognosis [11]. PD-1 is an immune checkpoint that can be applied clinically. After binding to its receptors, PD-1 reduces the activity of T cells and mitigates damage to healthy cells. The mechanisms associated with PD-1 can affect its expression, and the functionality of toxic T cells will be limited with regards to the control of tumor immunity [12, 13]. Karelizumab is a PD-1 inhibitor; after binding to PD-L1 on the surface of T lymphocytes and other cells, karelizumab will reduce mediated immunosuppression, activate more T cells, generate immune checkpoints, and kill tumor cells [14, 15]. Karelizumab can prolong a patient's survival time, control the spread and metastasis of tumor cells, and reduce angiogenesis.

In this study, we found that there was no significant difference between the two groups with regards to adverse reactions. Following treatment, the levels of VEGF, MMP-9, CEA, AFP, CA125, CD8+ and CA19-9 in patients from the observation group were lower than those in the control group, while the levels of CD3+, CD4+, CD4+/CD8+ were higher, thus indicating that the combination of TP chemotherapy and karelizumab had more advantages and obvious effects than TP chemotherapy alone. VEGF exerts significant impact on endothelial cell division and new angiogenesis. MMP-9 is a matrix degradation factor that can generate catalytic enzymes that exert impact on extracellular matrix degradation and accelerates endothelial cell transfer. Therefore, in this study, the levels of VEGF and MMP-9 in the observation group were lower than those in the control group, thus showing that karelizumab can effectively reduce the levels of these two factors. These

TABLE 5. Analysis of T lymphocyte subgroups.

Indicators	Time	Observation group (n = 48)	Research group (n = 48)	*t*	*p*
CD3+ (%)					
	Before treatment	50.24 ± 4.16	50.26 ± 4.19	0.023	0.981
	After treatment	65.25 ± 5.76	61.14 ± 5.16	3.682	<0.001
	t	14.636	11.34		
	p	<0.001	<0.001		
CD4+ (%)					
	Before treatment	32.56 ± 3.68	32.62 ± 3.75	0.079	0.937
	After treatment	44.95 ± 5.02	40.15 ± 4.58	4.894	<0.001
	t	13.791	8.813		
	p	<0.001	<0.001		
CD8+ (%)					
	Before treatment	35.68 ± 3.05	35.62 ± 3.08	0.096	0.924
	After treatment	21.56 ± 1.58	25.58 ± 1.95	11.097	<0.001
	t	28.48	19.081		
	p	<0.001	<0.001		

CD: cluster of differentiation.

effects exert impact on a patient's immunity system and can reduce angiogenesis by significantly controlling the growth of tumor cells and avoiding large-scale invasion and other conditions [16–18]. The levels of tumor markers mainly reflect the development of tumor cells. An increase in these levels indicates that a tumor is developing and there will be poorer prognosis [19, 20]. CD3+ is a T lymphocyte subtype and represents an indicator with which to test immune function. A reduction of CD3+ and CD4+, and an increase of CD8+ indicate a reduction in immune function. In our analyses, there was a clear improvement in the T lymphocyte subgroups and tumor markers of patients in the observation group, thus indicating that karelizumab can reduce the levels of tumor markers. In addition, this treatment regimen also improved the number of T lymphocyte subgroups. Thus, this strategy can regulate the body's immunity system to prevent and control the development of tumor cells. Karelizumab can block the combination of PD-1 and PD-L1, improve the ability of T cells to kill tumor cells, and limit the development of tumors [21–23]. The combination of karelizumab with TP chemotherapy did not significantly increase adverse reactions, thus indicating that karelizumab was relatively safe; the main reason for this is that only a short period of treatment was required. During drug treatment, patients did not experience serious adverse reactions and the negative effects of this treatment on patients was within the tolerable range [24, 25].

5. Conclusions

In conclusion, it is very difficult to treat advanced forms of ovarian cancer. After cytoreductive surgery, the administration of TP chemotherapy combined with karelizumab can regulate the levels of tumor markers and T lymphocyte subgroups; furthermore, this treatment proved to be safe and tolerable for the patient. This treatment regimen can be selected according to the individual situation of each patient.

AVAILABILITY OF DATA AND MATERIALS

The authors declare that all data supporting the findings of this study are available within the paper and any raw data can be obtained from the corresponding author upon request.

AUTHOR CONTRIBUTIONS

JHZ, YJS and GHD—designed the study and carried them out; supervised the data collection, analyzed the data, interpreted the data, prepare the manuscript for publication and reviewed the draft of the manuscript. All authors have read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval was obtained from the Ethics Committee of Affiliated Jiangyin Hospital of Nantong University (Approval no. 2023-036). Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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